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Systematic review with meta-analysis: the significance of histological disease severity in lean patients with nonalcoholic fatty liver disease

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Summary

Background: Current evidence suggests that lean and obese patients with nonalcoholic fatty liver disease (NAFLD) share an altered metabolic and cardiovascular profile. However, there is an incomplete understanding of the natural history of "lean-NAFLD." Indeed, an unanswered question is whether lean (BMI $\leq$ 25 Kg/m^2) NAFLD-patients are protected from severe histological outcomes.

Aim: To perform a meta-analysis with the goal of providing a quantitative estimation of the magnitude of fibrosis, as well as histological features associated with the disease severity, in lean versus overweight/obese-NAFLD patients.

Methods: Through a systematic search up to July 2017, we identified eight studies that compared histological outcomes in lean (n = 493) versus overweight/obese (n = 2209) patients.

Results: Relative to lean-NAFLD, overweight/obese-NAFLD patients showed significantly (P = .032) higher fibrosis scores; the observed difference in means between the two groups, which is the absolute difference between the mean value of fibrosis score [0-4] $\pm$ standard error, was 0.28 $\pm$ 0.13. The risk of having nonalcoholic steatohepatitis-NASH (OR 0.58 95% CI 0.34-0.97) was significantly lower in lean-NAFLD (n = 322) than in overweight/obese-NAFLD (n = 1357), P = .04. Relative to lean-NAFLD, overweight/obese-NAFLD patients also have significantly greater NAFLD activity (difference in means $\pm$ SE: 0.58 $\pm$ 0.16, P = .0004) and steatosis (difference in means $\pm$ SE: 0.23 $\pm$ 0.07, P = .002) scores.

Conclusions: Lean-NAFLD patients tend to show less severe histological features as compared to overweight/obese-NAFLD patients. Subsequent longitudinal assessment is needed to understand the clinical impact of these findings; however, the significant ~ 25% increment of mean fibrosis score in overweight/obese patients suggests that obesity could predict a worse long-term prognosis.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr. Y. Yuan. The Handling Editor for this article was Prof. Stephen Harrison, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

The prevalence of nonalcoholic fatty liver disease (NAFLD) has increased globally,[1] paralleling the figures of obesity and type 2 diabetes.[2,3] These three clinical conditions, also referred to as comorbidities, cluster together in the metabolic syndrome (MetS) along with cardiovascular disease (CVD).[4] Nevertheless, obesity constitutes a key determinant of awareness of liver disease due to the known risk-adverse association between obesity and NAFLD; both diseases reflect common—environmental—risk factors, including diet and lifestyle.[1] However, NAFLD can also occur in lean (nonobese) people;[5-7] the term "lean-NAFLD" is commonly used to describe this association.

The growing prevalence of NAFLD in Asia has contributed, in part, to the recognition of lean-NAFLD due to around 8%-19% of Asians with body mass index (BMI) less than 25 kg/m^2 have also been found to have NAFLD.[8] It is now clear, however, that lean-NAFLD also exists in western countries, as demonstrated in the results of the national health and nutrition examination survey III (NHANES III) that showed a prevalence of ~ 7% of lean-NAFLD in the United States population.[9]

Unfortunately, being slim (nonobese) does not necessarily mean one is healthy; in fact, being lean does not always lead to a lower risk of diabetes,[10] CVD,[11] or even NAFLD, as recently suggested.[5,12] In a large recent meta-analysis, we demonstrated that lean and obese patients with NAFLD share a common altered metabolic and cardiovascular profile.[5] Our observations, indeed, uncovered that lean-NAFLD patients are not necessarily "healthy lean," or "free of fat" because relative to lean-non-NAFLD people, lean-NAFLD individuals showed an excess of abdominal adipose tissue, probably as the leading cause of their NAFLD.[5]

Nevertheless, while the risk factors of NAFLD in lean patients have been partially clarified,[5] knowledge of the natural history of "lean-NAFLD" is not only poorly understood, but also remains controversial. In addition, the question of whether non-obese patients are protected from severe histological outcomes has not been completely elucidated. It is plausible to speculate that co-existing diseases, such as obesity and NAFLD, are prone to worsening the prognosis. However, it has not been established whether the presence of one or several of the above-mentioned comorbidities contributes to NAFLD disease severity, including fibrosis. The purpose of the present meta-analysis was to provide a quantitative estimation of the magnitude of fibrosis, as well as histological features associated with the disease severity, in lean-NAFLD versus overweight/obese-NAFLD patients.

2 | METHODS

We followed the appropriate methods for conducting a meta-analysis of observational studies (MOOSE)[13] (Table S1).

2.1 | Search strategy

We searched for published studies on MEDLINE (via-PubMed), Google Scholar, and The Cochrane Library, including The Cochrane Central Register of Controlled Trials, using the following keywords and terms in the title or abstract: "lean nonalcoholic fatty liver disease" and "nonobese nonalcoholic fatty liver disease;" details on the Boolean search are disclosed in the Supplementary Material section. In addition, we checked the reference section of all retrieved articles for additional literature sources, and the PubMed link "related articles" was used to identify potentially relevant papers. The literature search included all studies published before July 2017 and we imposed no country restrictions. The authors reviewed all abstracts independently to determine the alignment with the eligibility criteria, or to establish the appropriateness of the research topic. If these criteria were met, the authors retrieved the article and reviewed it in its entirety. There were no discrepancies in this process; details on data search/collection are summarised in Figure S1.

2.2 | Inclusion and exclusion criteria and data collection

The following inclusion criteria were considered when assessing the eligibility of the identified studies:

1. Observational studies (cross-sectional or longitudinal studies of which baseline data was retrieved) that included patients with a histologically confirmed diagnosis of NAFLD, in which comparisons between lean and overweight/obese patients were performed.
2. A clear definition of lean and non-lean (overweight / obese) patients with NAFLD, expressed as a BMI cut-off, which allows for the identification of two groups of patients: lean patients with NAFLD, defined as patients with a BMI $\leq$ 25 versus non-lean (overweight / obese) patients with NAFLD, defined as patients with BMI > 25.
3. A clear exclusion of co-existing common chronic liver diseases and secondary causes of steatosis, including heavy alcohol consumption, total parenteral nutrition, hepatitis B and C virus infection, and the use of drugs known to precipitate steatosis.

For each study, we retrieved the following information for inclusion in the meta-analysis: (1) histological features: fibrosis score, proportion of patients with NASH/ non-NASH in each group (lean and overweight/obese), NAFLD Activity Score (NAS) and steatosis score; (2) demographic features (age, sex, country of origin as proxy of ethnicity); (3) study design and (4) anthropometric variables (waist circumference) and homoeostatic model assessment-insulin resistance (HOMA-IR)—whenever available. All quantitative variables had to be expressed as mean $\pm$ standard deviation (SD); prior to the analysis, we converted the standard error (SE) or interquartile range to SD, whereas the median was converted to mean.

The following exclusion criteria were also considered when assessing the eligibility of the identified studies: (1) Studies pertaining to patients with NAFLD in which the authors failed to specify the BMI categories utilised, as explained above (lean vs non-lean); (2) duplicate publications; (3) unpublished papers (*only* full-text journal articles *were included)* and (4) papers that included data on NAFLD patients using a non-standard definition of lean subjects.

2.3 | Statistical analysis

A random effect model was adopted when summarising statistical synthesis. This model assumes that the treatment effect is not the same across all studies included in the analysis.

To specifically provide measures of the absolute difference between the mean values of the explored histological variables (fibrosis score F0-F4, NAFLD Activity Score, and steatosis score 0-3) calculated for two groups (lean vs overweight/obese) we used the difference in means. This approach was justified, as we used outcome measurements on the same scale/unit performed by the same method as described below.[14] For the dichotomous variable (NASH / non-NASH), the effect denotes odds ratio (OR) and corresponding 95% confidence interval (CI).

For each analysis, we generated a forest plot to display results; as we hypothesised that ethnicity may provide an important source of variability, we also stratified the estimate of the average effect of the studies by ethnicity. Details regarding subgroup analyses, meta-regression and heterogeneity are fully disclosed in the Supporting information. We performed all calculations using the Comprehensive Meta-Analysis computer program (BIOSTAT, Englewood, NJ, USA).

2.4 | Assessment of study quality

The quality of the studies included in the meta-analysis was assessed using The Newcastle-Ottawa Scale (NOS) (see Table S2).

3 | RESULTS

3.1 | Study selection

We retrieved 33 studies that were initially identified using the search strategy described in Figure S1 as potentially relevant for the present investigation. We subsequently excluded 25 studies because they did not meet the inclusion criteria: (1) in two cases, the authors used a non-conventional definition of a lean individual based on a non-standard BMI cut-off value (BMI < 30),[6,15] and (2) 23 studies were population-based reports in which NAFLD was diagnosed non-invasively by imaging techniques or laboratory data, as we previously explained.[5]

3.2 | Study characteristics

Thus, we included the remaining eight hospital-based studies that met the inclusion criteria,[5,16-22] including a total of 2702 adult-patients of both sexes with NAFLD, in the present meta-analysis. One study belongs to our population that took part in an earlier lean-NAFLD meta-analysis on epidemiological risk factors.[5]

We obtained scores of liver fibrosis from one study through contact with the study authors, who generously provided details to calculate the pooled effect.[18]

Four studies were based on a Caucasian population,[5,16,18,22] whereas the remaining four included an Asian population.[17,19-21] All the studies scored well in terms of the selection criteria, comparability of lean and overweight/obese NAFLD on the basis of the study design or analysis, and ascertainment of exposure (see Table S2); in all the studies, the setting was hospital-based.

There was no apparent selection bias in the indication of liver biopsy in lean or overweight/obese patients with NAFLD (Table 1); in all the studies, histological assessment was uniformly performed according to the NASH clinical research network system developed by Kleiner et al[14] The overall study characteristics, including histological variables are shown in Table 1.

3.3 | Histological disease severity in lean versus overweight / obese NAFLD: Being overweight / obese can raise the risk of NASH and is associated with a significant increase of the fibrosis score

The analysis of liver fibrosis, which was performed based on pooled data extracted from eight studies,[5,16-19,21,22] showed that overweight/obese patients (n = 2209) with NAFLD have significantly greater fibrosis scores than lean patients (n = 493) (P = .032, see Figure 1). Specifically, the observed difference in means between the two groups was 0.28 ± 0.13, which represents an increment of ~24.82% (over pooled mean fibrosis score of 1.128 in the lean group) in the mean of fibrosis score in overweight/obese-NAFLD patients relative to the mean of fibrosis score found in lean-NAFLD. Egger's regression intercept confirmed absence of publication bias (intercept −0.34, P = .83). However, we found substantial heterogeneity (I^2: 73.5, P = .0001) in the analysis of combined studies.

The estimate of the effect stratified by ethnicity (Asian vs Caucasian) is shown in Figure S2; the analysis suggests that the difference in the fibrosis score between lean and non-lean patients remained significant among Caucasians. Sub-group analysis showed that intra-group effect was homogeneous (Asian: I^2: 58, P = .068 and Caucasian I^2: 55, P = .083).

Although we found that the effect estimate varied among studies and the observed pooled point estimate of the difference in means ranged from 0.15 to 0.31, significant results remained after excluding one study at a time (see Figure S3).

We further explored the potential effect of covariate/s that could explain the observed difference in the fibrosis score between lean and overweight/obese patients. Meta-regression analysis did not reveal any significant correlation between differences in age (slope: 0.03, P = .27), HOMA-IR (slope: 0.3, P = .09), or waist circumference (slope: 0.09, P = .49) and liver fibrosis. Nevertheless, the

TABLE 1 Histological features of patients included in the meta-analysis: lean versus non-lean (overweight/ obese)

Author, Country	Sample size (lean/ overweight/ obese)	Indication of liver biopsy	NASH/ no-NASH lean (n)	NASH/ no-NASH obese (n)	Fibrosis score (mean ± SD)		NAFLD activity score (NAS) (mean ± SD)	
					Lean	Obese	Lean	Obese
Akyuz,[16] Turkey	37/446	Unclear, retrospective analysis.	-	-	0.33 ± 0.74	1 ± 1.48	4.67 ± 3.7	5 ± 1.48
Alam,[17] India	56/164	Abnormal liver enzymes.	30/26	77/87	1.2 ± 0.8	1.1 ± 0.8	4.4 ± 1.4	4.4 ± 1.1
Kumar,[20] India	18/73	Unclear, lack of details.	5/13	36/37	1.52 ± 1.0	2 ± 1	3.3 ± 1.5	4.1 ± 1.4
Fracanzani,[18] Italy	143/526	Abnormal liver enzymes and /or additional risk factors, including IR	25/118	215/311	0.7 ± 0.95	1.43 ± 1.17	2.7 ± 1.6	3.9 ± 1.7
Honda,[19] Japan	134/406	Evaluation of NAFLD severity	-	-	1.6 ± 1.1	1.7 ± 1.0	3.5 ± 1.6	4.2 ± 1.5
Leung,[21] Hong Kong	72/235	Abnormal liver enzymes, evaluation of NAFLD severity, enrolment in clinical trials.	30/42	121/114	1.3 ± 1.5	1.7 ± 1.4	3.3 ± 1.3	3.8 ± 1.2
Margariti,[22] Grece	8/48	Patients who consented to the biopsy.	4/4	33/15	1.5 ± 1.7	1.5 ± 1.2	3.1 ± 1.9	4.0 ± 1.9
Sookoian,[5] Argentina	25/311	Abnormal liver enzymes and /or additional risk factors, including IR.	12/13	181/130	0.6 ± 0.96	0.87 ± 1.22	3.37 ± 1.99	3.71 ± 1.41

The presence of NASH, fibrosis and NAFLD activity score (NAS), were assessed in all the studies according to the NASH clinical research network system developed by Kleiner et al.[14]

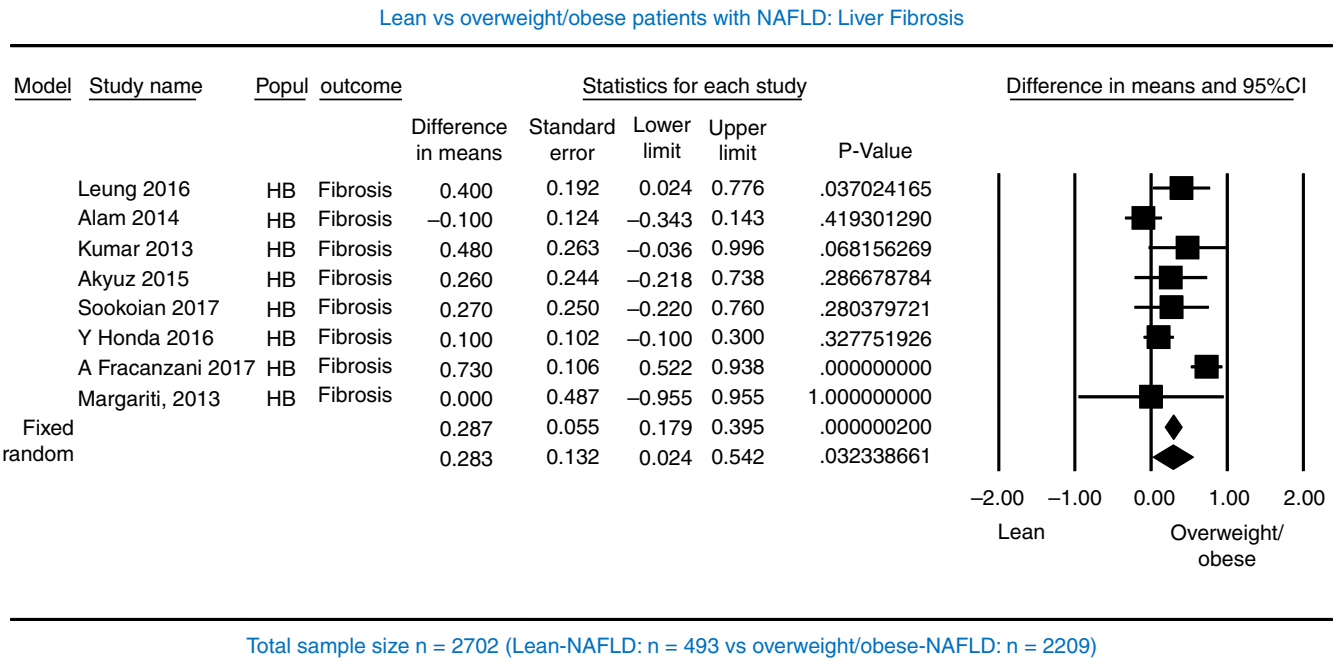

FIGURE 1 Association analysis of liver fibrosis in lean-NAFLD patients versus overweight/obese - NAFLD patients. The effect indicates the difference in means, which is the absolute difference between the mean value of fibrosis score [0-4], standard error, and the corresponding lower and upper limits (95% confidence interval), according to the status of lean (non-obese) versus overweight/obese. The first author of the study and the year of publication are shown under the sub-heading: "study name." Popul: indicates design features (HB: hospital-based). In the graph, the filled squares denote the effect of individual studies, and filled diamonds express combined fixed and random effects

results of meta-regression must be taken with caution because the number of studies[5,16,18,19,21] included in the analysis of clinical co-variables was small.

The presence of NASH in lean versus overweight/obese patients with NAFLD was assessed based on information extracted from six studies (n = 1679)[5,17,18,20-22] that reported the proportion of patients with diagnosis of NASH and non-NASH. We found that the risk of having NASH (OR 0.58 95% CI 0.34-0.97) was significantly lower in lean (n = 322) than in overweight/obese patients with NAFLD (n = 1357) (P = .04, see Figure 2). While no publication bias was noted (intercept 0.178, P = .92), we observed substantial and significant heterogeneity (I^2: 66.5, P = .01).

Sub-group analysis comparing Asian vs Caucasian showed that the difference in the proportion of NASH patients in lean vs. overweight/obese remained significant among Caucasians (Figure S4). Stratification according to ethnicity showed lack of intra-group heterogeneity (Asian: I^2: 54, P = .11 and Caucasian: I^2: 24.7, P = .26). Figure S5 shows the impact of each study on the combined pooled effect.

Likewise, the analysis of NAFLD activity score (NAS) that was based on results from eight studies[5,16-22] showed that lean-NAFLD patients have significantly lower mean score as compared to overweight/obese NAFLD patients (difference in means ± SE: 0.58 ± 0.16, P = .0004) (Figure 3); we found no publication bias (intercept −0.68, P = .74).

We observed a significant heterogeneity (I^2: 74.9, P = .0001) that could not be explained by ethnicity (Asian: I^2: 69, P = .021 and Caucasian: I^2: 71.8, P = .014), Figure S6. Sub-group analysis within Asian and Caucasian showed that the difference in the NAS score between lean and overweight/obese patients was significant in both ethnic groups.

The one-study-removed analysis (Figure S7) shows consistency of the effect across the studies, and suggests a robust association between the NAS score and the lean/ overweight-obese status. Meta-regression analysis results suggested that HOMA-IR (slope: 0.42, P = .013), but not age (slope: 0.01, P = .8) or waist circumference (slope: 0.14, P = .58) would explain the observed difference in the NAS score, although this result should be interpreted with caution because there was limited information on clinical and biochemical co-variables to be incorporated into the analysis.

Finally, five studies (n = 1886)[5,16,17,19,21] without evidence of heterogeneity (I^2: 46.5, P = .11) or publication bias (intercept −1.05, P = .58) disclosed data of steatosis score according to lean and overweight/obese patients. The analysis showed that relative to overweight/obese NAFLD patients (n = 1562), lean-NAFLD (n = 324) patients have significantly (P = .0023) lower steatosis scores (difference in means 0.23 ± 0.07) (Figure 4).

4 | DISCUSSION

4.1 | Summary of main findings

Based upon the results yielded by the meta-analysis of eight studies, which included data of histological outcomes in lean versus overweight/obese patients with NAFLD, we demonstrated that relative to overweight/obese-NAFLD patients, lean patients have less severe

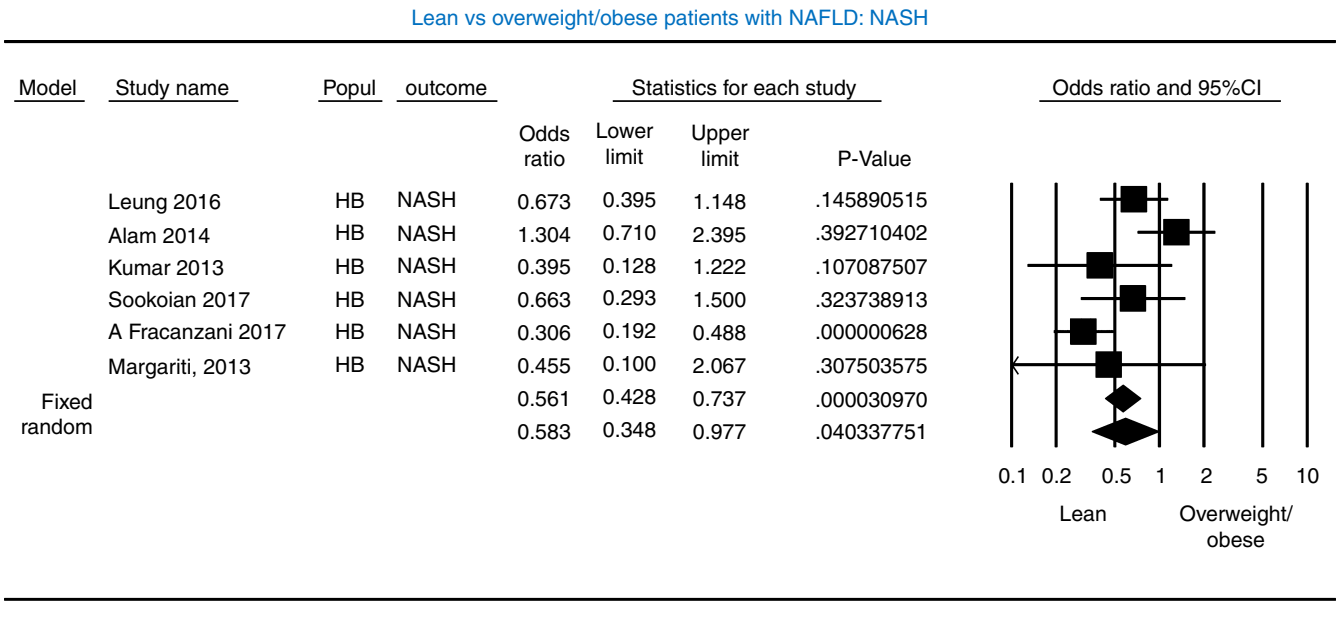

FIGURE 2 Association analysis of NASH in lean-NAFLD patients versus overweight/obese -NAFLD patients. The effect indicates OR (Odds ratio) and the corresponding lower and upper limits (95% confidence interval), according to the status of lean (non-obese) and overweight/obese. The first author of the study and the year of publication are shown under the sub-heading: "study name." Popul: indicates design features (HB: hospital-based). In the graph, the filled squares denote the effect of individual studies, and filled diamonds express combined fixed and random effects

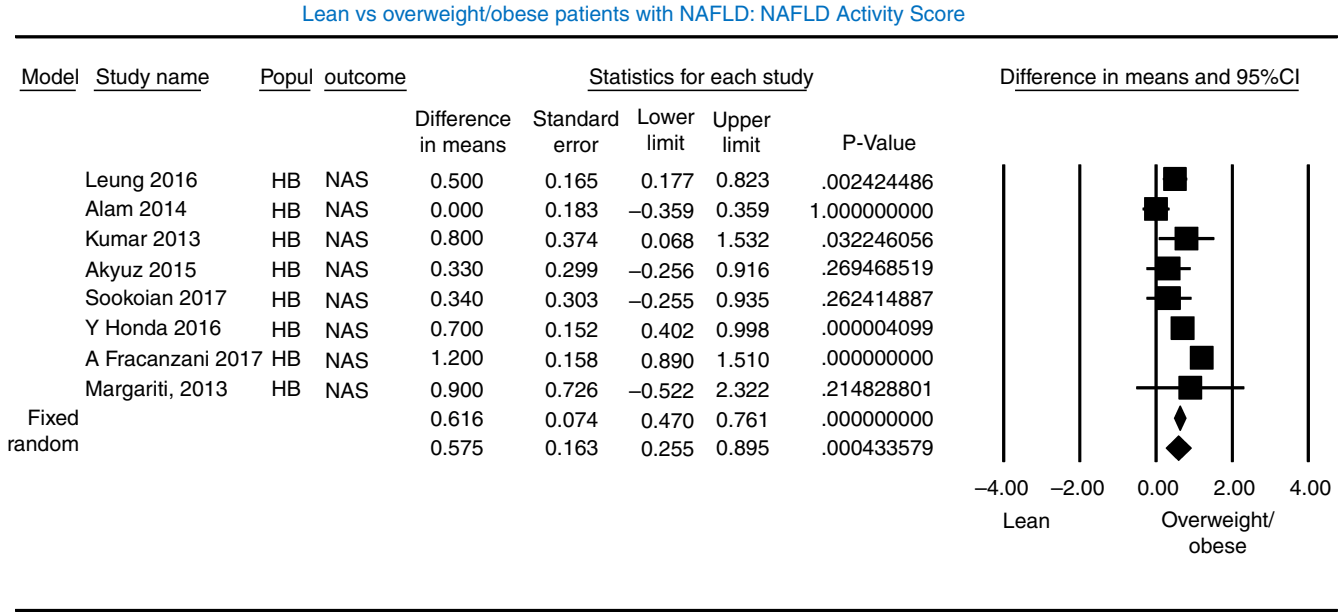

FIGURE 3 Association analysis of NAFLD activity score (NAS) in lean-NAFLD patients versus overweight/obese -NAFLD patients. The effect indicates the difference in means, which is the absolute difference between the mean value of NAS score, standard error, and the corresponding lower and upper limits (95% confidence interval), according to the status of lean (non-obese) versus overweight/obese. The first author of the study and the year of publication are shown under the sub-heading: "study name." Popul: indicates design features (HB: hospital-based). In the graph, the filled squares denote the effect of individual studies, and filled diamonds express combined fixed and random effects

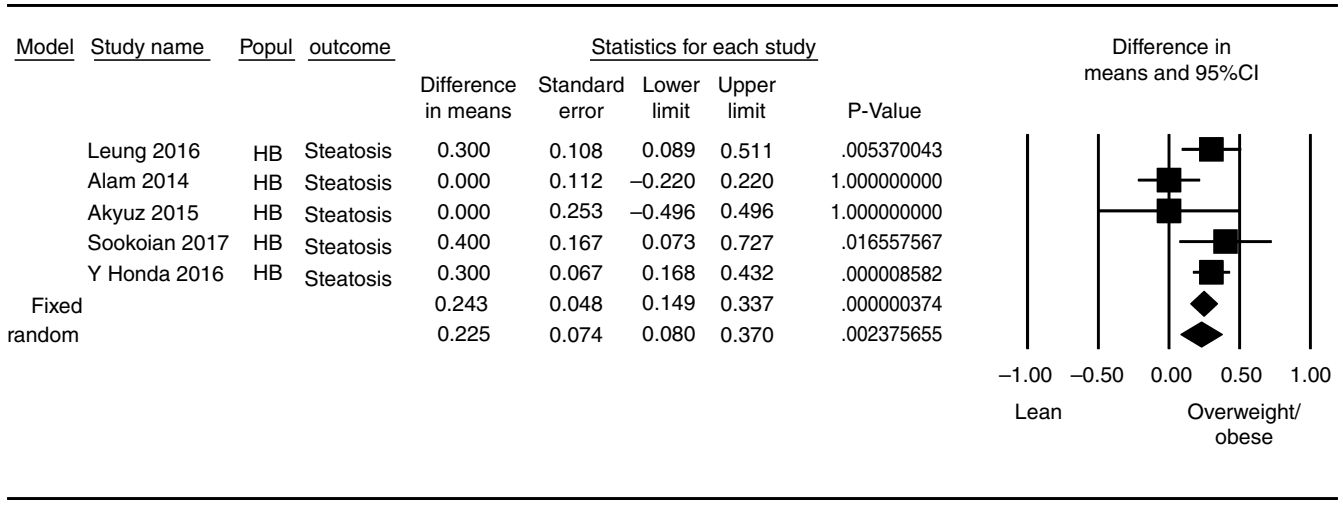

FIGURE 4 Association analysis of steatosis score in lean-NAFLD patients versus overweight/obese -NAFLD patients. The effect indicates the difference in means, which is the absolute difference between the mean value of steatosis score [0-3], standard error, and the corresponding lower and upper limits (95% confidence interval), according to the status of lean (non-obese) versus overweight/obese. The first author of the study and the year of publication are shown under the sub-heading: "study name." Popul: indicates design features (HB: hospital-based). In the graph, the filled squares denote the effect of individual studies, and filled diamonds express combined fixed and random effects

histological disease. Specifically, we found that lean patients are less likely to have NASH. While both groups of patients presented a substantial proportion of NASH (33% and 49% of lean and overweight/obese-NAFLD patients, respectively, had NASH), the two groups showed a different degree of histological scores. Consequently, the disease progression in lean versus overweight/obese NAFLD could not necessarily be identical. For instance, overweight/obese-NAFLD patients tended to show a modest, but significant, increase in the mean fibrosis score, as well as greater NAFLD activity and steatosis scores when compared to lean-NAFLD patients. Furthermore, we

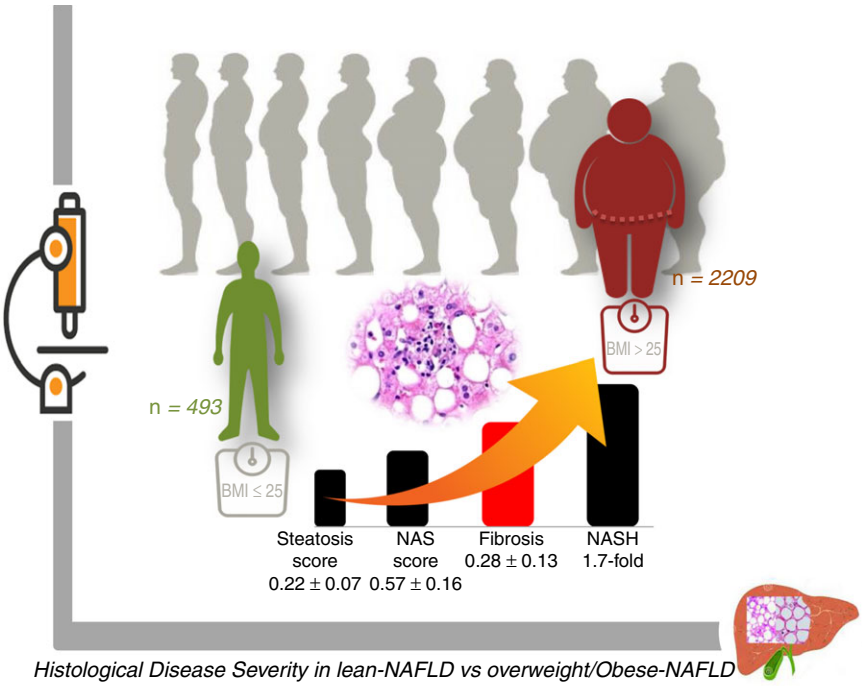

FIGURE 5 Histological disease severity in lean versus overweight/obese NAFLD: Being overweight/obese can raise the risk of NASH by 1.7-fold. The image illustrates the results yielded by the meta-analysis of histological features of NAFLD in lean and overweight/obese patients. Relative to lean-NAFLD, overweight/obese NAFLD patients tend to show a modest increase in scores of histological outcomes associated with the disease severity, including liver fibrosis. The effect is indicated as the difference in means ± standard error

observed a *protective* association between the lean status and the risk of NASH (OR 0.58 95% CI 0.34-0.97), which was explored in a sample of 1679 patients. A summary of the findings of our study is shown in Figure 5.

4.2 | Limitations and strengths at study, outcome, and review levels

Nevertheless, some limitations to our study should be noted, which are implicit in the studies included in the meta-analysis. For instance, it remains unclear whether the differences in the histological outcomes between the two groups of patients can be explained by the condition of being "lean" or "overweight/obese." In fact, other co-variables might have significantly influenced the severity of fibrosis or NASH, including age, the presence of insulin resistance and/or visceral adiposity. Unfortunately, limitations of the published studies that failed to disclose data of HOMA-IR or waist circumference according to lean and overweight/obese -NAFLD[17,20,22] prevented us from a proper meta-regression analysis to assess the potential effect of modifiers' or covariates. Even when considering these limitations, it is worth noting that differences in HOMA-IR could account for differences in the NAFLD activity score (NAS) between the two groups which were consistent with previously reported clinical-morphological correlations.[23,24]

While there was heterogeneity in the overall results, the effects were homogeneous in the analysis stratified by ethnicity. In fact, the observed difference in the fibrosis score and NASH proportion seems to be restricted to the studies that included Caucasian population.

On the contrary, differences in the NAS score between lean and non-lean could not be explained by sub-groping analysis of the studies according to ethnicity or other relevant characteristics.

It is unlikely that either the observed heterogeneity or the differences according to ethnicity can be explained by methodological diversity, which represent variability in study design, because all the studies were hospital-based. Nevertheless, bias in the selection of patients cannot be ruled out as the reason/s of indicating the liver biopsies were not necessarily homogeneous among the studies (Table 1). Authors of some studies explained that liver biopsy was indicated to patients who had either persistently elevated levels of aminotransferases[17] or abnormal liver test and /or additional risk factors for NASH, including insulin resistance or MetS,[5,18] while in other studies, authors explained that regardless of the biochemical profile, they conducted a liver biopsy on all patents with NAFLD for the purpose of diagnosing and staging of NASH.[19,21] Furthermore, the observed heterogeneity and ethnic differences might be both attributed to variability in the participants, which is known as clinical diversity. This source of variability includes, but is not restricted to, dietary and environmental factors, and genetic predisposition.[19,21,25]

A note of caution should be added because we included information of histological outcomes in overweight and obese individuals as a single category. Unfortunately, none of the studies but one report[20] provided data of overweight subjects as a separate group; therefore, we were unable to estimate putative differences between overweight and obese NAFLD-patients. As a remarkable aspect, none of the studies included morbid obese patients, who are known to present different histological features that would have introduced bias in the analysis of overweight/obese group; Figure S8 shows mean values of BMI (kg/m^2) according to lean and non-lean study participants.

Likewise, the lean group could have been sub-stratified into underweight and normal weight[8]; in fact, these two sub-groups

could represent NAFLD patients in whom the disease would be linked to different underlying mechanisms, for example malnutrition/ malabsorption. Hence, the ideal study should contemplate at least five different categories, including underweight, normal weight, overweight, obese and morbid obese.[8] Nevertheless, this approach not only requires a special strategy for performing inter-group comparisons (e.g., network meta-analysis) but should guarantee an adequate sample size per group, which represents an enormous challenge.

On the other hand, it can be argued that a BMI cut-off point for defining overweight/ obese should not be >25 kg/m^2 in individuals from Asia, where a BMI cut-off of 23 kg/m^2 is recommended.[8] Unfortunately, all studies from Asia but the report of Kumar et al[20] used a BMI < 25 kg/m^2 to define lean subjects.

It should be also argued that NAFLD is not invariably associated with the presence of features of the metabolic syndrome.[26] The study of Akyuz and coworkers showed that hemoglobin level is an independent predictor of NASH severity not only in lean patients[16] but also NAFLD patients without obesity and insulin resistance.[26] Therefore, lean-NAFLD could represent a different clinical entity, the pathogenesis of which could be mediated by other mechanisms, for instance, microbial dysbiosis,[27] extra-hepatic underlying diseases,[28] sarcopenia,[29] or polycystic ovary syndrome with hyperandrogenism.[30]

Finally, there were two studies for which the total sample size (lean-NAFLD and overweight/obese NAFLD) was small (fewer than 100 patients).[20,22] Thus, it can be argued that small-study-effects might have introduced bias into the pooled analysis. Nevertheless, no publication bias was observed in any of the assessed histological outcomes. Most importantly, we performed "conservative" random-effects analysis, which assumes that the effect sizes are heterogeneous and sampled from a distribution of population effect sizes. In addition, the one-study-removed analysis consistently demonstrated that the effect was in the same direction in all the studies, including those studies that might be regarded as underpowered (Figures S3, S5, and S7). For instance, the difference in means of fibrosis score between lean and overweight/obese patients with NAFLD was 0.25 ± 0.14 and 0.29 ± 0.13 in the study of Kumar[20] and Margariti,[22] respectively, which is comparable to that of the observed pooled effect (Figure 1).

The main strength of this study, however, stems from the relatively large sample size that was subjected to the analyses (data from 2702 patients with NAFLD in whom the disease was characterised by liver biopsy). Likewise, the magnitude and direction of the effects of all the histological outcomes were consistently noted in both, Asians and Caucasians. Interestingly, there was a remarkable uniformity in the scoring system used for the histological assessment, which was in all the studies the system developed by Kleiner et al[14] Finally, rather than using the fixed-effect model, we calculated all the effect sizes on the bases of the random-effect model, which permit generalisations that extend beyond the studies included in a systematic review.[31]

4.3 | Implications for clinical practice and future research

The results of this meta-analysis suggested that overweight/obese patients with NAFLD when compared to lean ones are ~ 1.71-fold more likely to have NASH. This conclusion can be also expressed from the perspective of being lean (nonobese), which reduces the occurrence of NASH by ~ 40% (OR: 0.58). In addition, overweight/obese patients with NAFLD showed a significant increment of ~ 24.8% in the mean of fibrosis score, and a modest increase of ~16.8% and 13.7% in the mean of NAFLD activity and steatosis score, respectively, when compared to lean-NAFLD. Taken together, the findings regarding liver fibrosis could be of critical importance in the prognosis and long-term clinical consequences of overweight/obese NAFLD patients. For example, fibrosis stage, but not steatosis and lobular inflammation grade, or NAS categories of the NAFLD score, have been previously associated with liver and non-liver related- mortality.[32-34] In addition, fibrosis stage (from fibrosis F0 to F4) was independently associated with liver-related mortality in a large longitudinal study of patients with NAFLD, in which the difference in the fibrosis score imposed an incremental score-dependent hazard-risk of negative outcomes (death or liver transplantation) that escalated from 1.88 (F1) to 2.89 (F2) to 3.76 (F3) to 10.9 (F4) compared to stage F0.[32] It is then reasonable to speculate that an increment of ~25% in the mean of fibrosis score is not negligible, but, rather, potentially imposing considerable long-term impact on the natural history of the disease. Unfortunately, among the studies included in our meta-analysis, there was only one remarkable report from Hong-Kong in which the authors performed longitudinal assessment of lean versus overweight/obese patients with NAFLD.[21] In this study, Leung et al observed a higher frequency of clinical events, including cardiovascular disease and death, in obese-NAFLD than in lean-NAFLD.[21]

Therefore, whereas a greater risk of NASH and an increased mean fibrosis score among overweight/obese patients are both expected to have strong clinical impact, it should be highlighted that the studies included in our meta-analysis provided us with cross-sectional data. Hence, assessment of the long-term clinical consequences of the histological outcomes in lean versus overweight/ obese patients should be guaranteed in further prospective studies. Whether the presence of overweight/ obesity intrinsically predicts the timing of referral to tertiary care then imposing differences in the timing of NAFLD diagnosis is not known; future longitudinal studies should also shed light on this issue.

In conclusion, the results of our cross-sectional study suggested that overweight/obese and lean-NAFLD patients while sharing all the risk factors of the MetS,[5] show differences in the histological disease severity. Overweight/obese NAFLD patients present a modest increase of overall scores of histological outcomes, including liver fibrosis, which could have substantial impact in the natural history of the disease, not to mention that relative to normal weight, obesity — regardless of whether it is associated with NAFLD— is, *per se*, associated with significantly higher all-cause mortality.[35] This conclusion, however, should not prevent physicians from the search of NASH or

fibrosis in lean-NAFLD patients, particularly when presenting with visceral obesity. Lean-NAFLD patients should also be considered as potential candidates for treatment with novel therapeutic strategies aimed to reverse NASH and/or liver fibrosis, because, as demonstrated in this study, they may also present advanced disease.

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AUTHORSHIP

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Author contributions: SS and CJP designed the study, performed the statistical analysis, analysed and interpreted the data, and prepared and wrote the manuscript. Both authors have read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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